**Imaging as a Biomarker: Standards for Change Measurements in Therapy**
14-15 September 2006, NIST, Gaithersburg, MD

# The Osteoarthritis Initiative (OAI): A Public-Private Partnership

Charles Peterfy, M.D., Ph.D.
Chief Medical Officer
Synarc, Inc.
San Francisco, CA

# Osteoarthritis is a Major Unmet Medical Need

- Highly prevalent, chronic, debilitating and costly
  - 8% of the US population (21 M people) have physician-diagnosed OA
    - Many more have undiagnosed or subclinical OA
      - 50% >65 years: frequent knee pain and X-ray OA
      - But, only 1 in 6 consult a physician
  - By 2020, 20% (70 M people) >65 y
    - ⇨ 35 M Americans with X-ray OA
  - >200,000 total knee replacement procedures for OA
- Only symptomatic therapy
- No preventative or disease-modifying therapies (DMOADs) with proven efficacy and safety

# Barriers to OA Drug Development

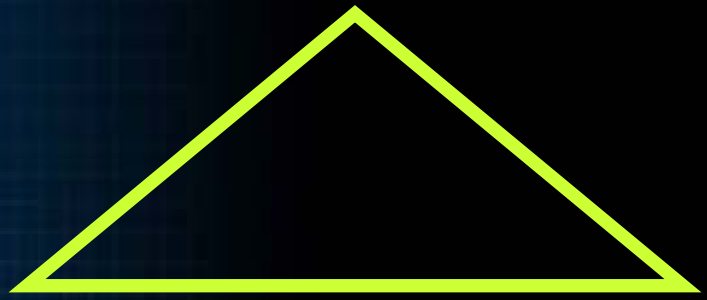
- Inadequate understanding of OA pathophysiology
  - Link between structural abnormalities and clinical outcomes
  - ⇨ Difficulty identifying potentially modifiable therapeutic targets
- Epidemiological studies and clinical trials to elucidate these have to be large, long, difficult and expensive
- Existing cohorts offer valuable info, but are too small and inaccessible
- Lack of biomarkers which are suitably valid, discriminative and feasible

# The Osteoarthritis Initiative: A Public-Private Partnership


## Academia

NIH funded contracts

Access to public database and specimens



## Industry

Study planning

Scientific input

Financial backing

Data & specimens

## Government

NIH: Financial input

Contract funding

Holder of public database

Specimen repository

FDA

# Goals of OAI

- Produce a public research resource
  - Identify and validate imaging, biochemical and genetic biomarkers for OA
  - Characterize early natural history and progression of OA
  - Evaluate risk and prognostic factors (including biomarkers) for OA onset and progression
- Main focus on knee OA
  - Limited data on hip and hand OA

# Approach to Meet OAI Goals

- Prospective cohort study of knee OA
  - Diverse and representative sample of people with knee OA or at risk of developing knee OA
  - Serial measurements (annual)
    - Imaging of knee, hip and hand
    - Biospecimens for biochemical and genetic markers
    - Clinical assessment (joint Sx, disability) and risk factors

⇨ Public data archive on the web

⇨ Archived images for distribution to users

⇨ Archived biospecimens available by application

# Infrastructure and Organization

- Government Partners
  - National Institute of Arthritis & Musculoskeletal and Skin Diseases (NIAMS)
    - Gayle Lester (Project Officer)
  - National Institute on Aging (NIA)
  - National Center for Complementary & Alternative Medicine
  - National Center on Minority Health & Health Disparities
  - National Institute of Biomedial Imaging and Bioengineering
  - National Institute of Dental & Craniofacial Research
  - Office of Research on Women's Health
  - Office of the Director, NIH

# Infrastructure and Organization

- Pharmaceutical Partners
  - GlaxoSmithKline
    - Christine Dabrowski and others
  - Merck & Company, Inc.
    - Chan Beals and others
  - Novartis Pharmaceuticals Corporation
    - Monica Luchi, and others
  - Pfizer, Inc
    - Marie Pierre Hellio LeGraverand-Gastineau, and others
  - *Provide funding and participate in scientific decisions*

# Infrastructure and Organization

- Clinical Centers
  - University of Maryland / Johns Hopkins University
    - Marc Hochberg, Joan Bathon
  - Memorial Hospital Rhode Island / Brown University
    - Charles Eaton, Timothy McAlindon
  - Ohio State University
    - Rebecca Jackson
  - University of Pittsburgh
    - Kent Kwoh
  - *Subject recruitment and enrollment*
  - *3.0 T Siemens Trio MR scanner installed at each center, dedicated to OAI*

# Infrastructure and Organization

- Data Coordinating Center
  - University California San Francisco (Michael Nevitt)
- Imaging QA Center
  - Synarc, Inc. (Charles Peterfy)
- Steering Committee
- Observational Study Monitoring Board (OSMB)
- Consultants and Subcontractors

# Imaging Work Group

- F. Boada
- W. Carter
- B. Dardzinski
- F. Eckstein
- J. Evelhoch
- D. Felson
- G. Gold
- B. Goodpaster
- M-P. Hellio Le Graverand
- M. Kothari
- P. Lang
- G. Lester
- M. Nevitt
- C. Peterfy
- T. Pellas
- C. Resnick
- D. Robertson
- E. Schneider
- L. Sharma
- G. Tung
- T. Woodworth

# Progression and Incidence Cohorts

Number

1,330

**Progression:**
Sx knee OA
at baseline

→ Follow for progression
(Sx, function, structure)

3,215

**Incidence:**
Risk factors for
Sx knee OA

→ Follow for incident
Sx knee OA and other
endpoints (X-ray OA)

190 incidents
expected

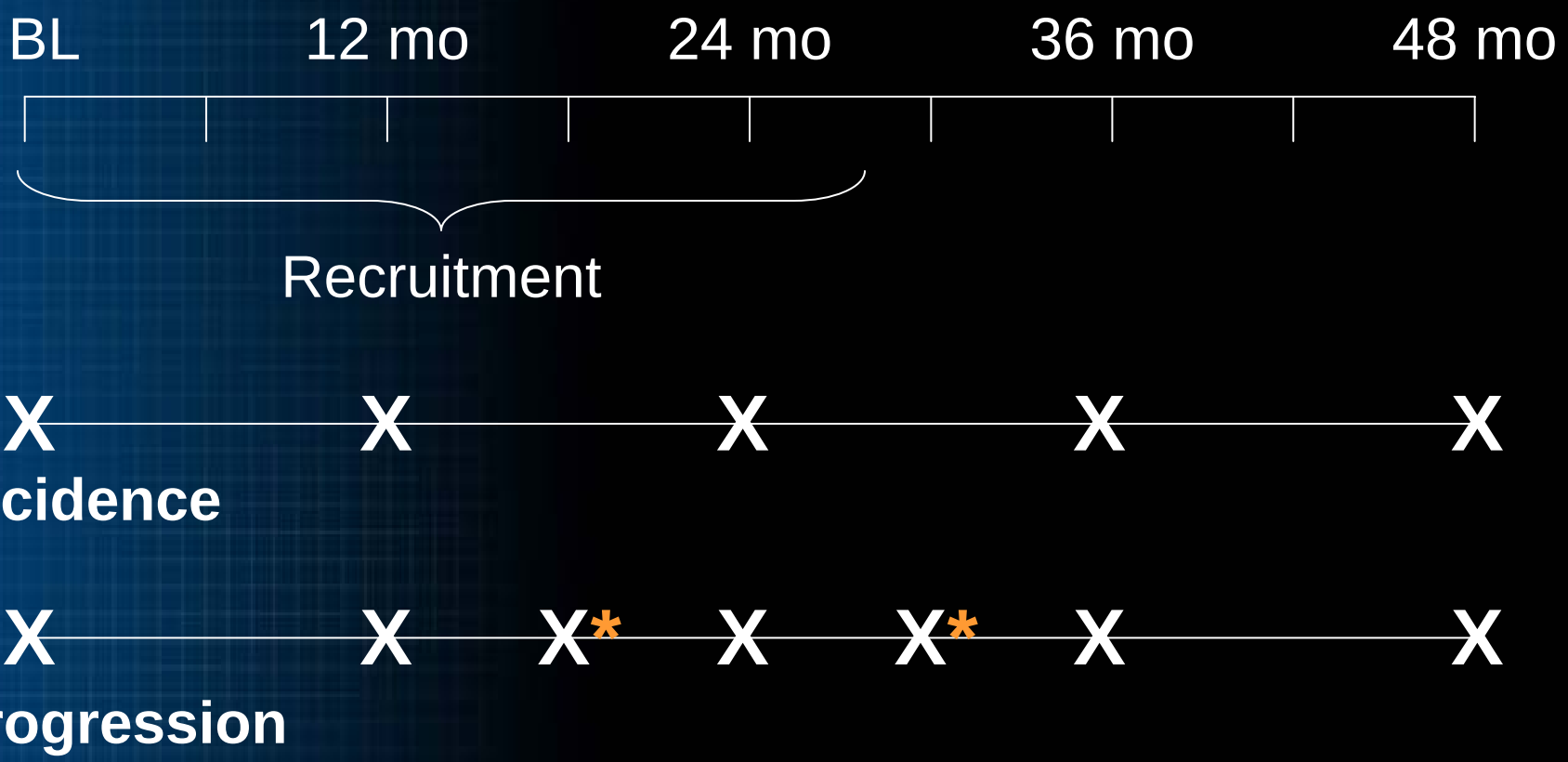
200

"Nonexposed" control group:
No Sx, no X-ray OA,
No risk factors

# Subjects: All Cohorts

- Inclusion
  - Men and Women
  - Ages 45 -79 years
  - All ethnic minorities (19%)
- Exclusion
  - Contraindications to MRI
  - History of inflammatory arthritis
    - RA Sx and medication screen
  - Bilateral end-stage disease (severe JSN and/or bilat TKR)

# Examination Schedule




- * 50% Progression cohort get 18 and 30 mo visits (MRI, biospecimens, Sx)

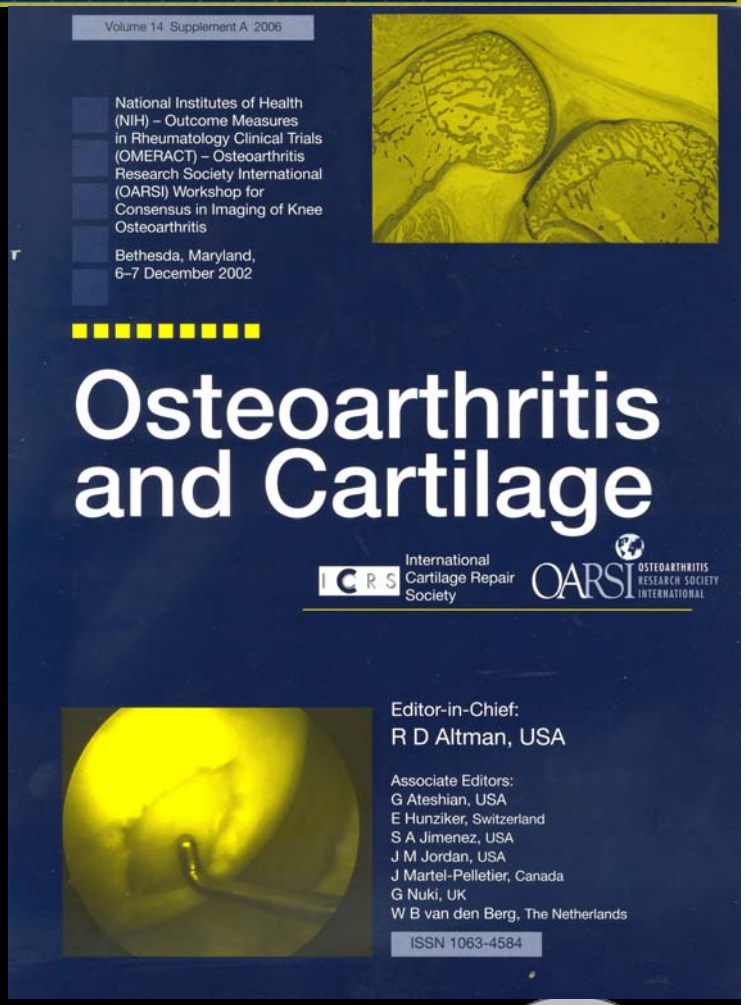
# Designing the Imaging Protocol

- Provide imaging data on as many joint structures and features believed to be relevant to OA as possible
- Provide images able to support as broad a range of existing and anticipated measurement methods for each structure and feature as possible
- Balance scientific requirements for image quality and consistency against practical needs of high throughput and patient retention

# MRI Protocol: Key Considerations

1. Which articular structures and OA features to focus?
   - Articular Cartilage
   - Osteophytes
   - Bone marrow edema
   - Menisci
   - Synovial effusion
   - Cruciate and collateral ligaments
   - Subarticular bone cysts
   - Periarticular bursa
   - Thigh muscles

OMERACT-OARSI Workshop for Consensus on OA Imaging, Bethesda, Dec 2002



# MRI Protocol: Key Considerations

2. What measurement methods (quantitative and semi-quantitative) to support for each?
    - Most established existing biomarkers:
        - Cartilage volume / thickness (regional)
        - Semiquantitative scoring of cartilage and other structures
            - e.g., WORMS
    - Should also support as many future analyses as possible

# MRI Protocol: Key Considerations

3. Subject tolerance
   - 60 min – *75 min*
4. Generalizability of the results
   - Availability of hardware and pulse sequences
     - Commercial systems and pulse sequences
   - Standardized vs. diverse systems and pulse sequences
     - Identical, dedicated, state of the art systems at each site
     - Standardized protocol
     - ⇨3T MRI (Siemens Trio): ↑ resolution / speed, avoid obsolescence
     - Extrapolation of 3T data to 1.5T data?
     - Could not borrow protocols established for 1.5T

# MRI Protocol: Key Considerations

5. Future utility
   - Images must support broadest range of analyses possible *now and tomorrow*

# Image Quality Control

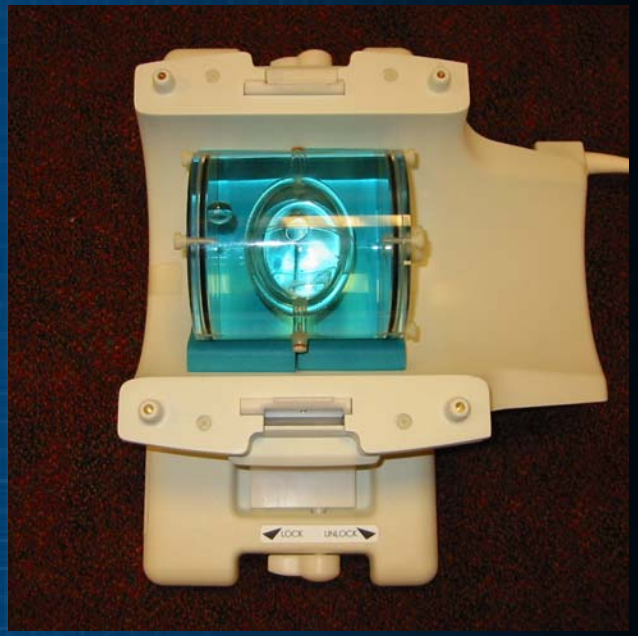
- Goals
  - Uniform high-quality artifact-free images from all sites
  - Longitudinal consistency of key parameters
    - SNR, CNR, signal homogeneity, spatial distortion
  - Comparability of images from all 4 sites
  - Minimum need for repeat imaging by preemptive correction of slowly developing problems

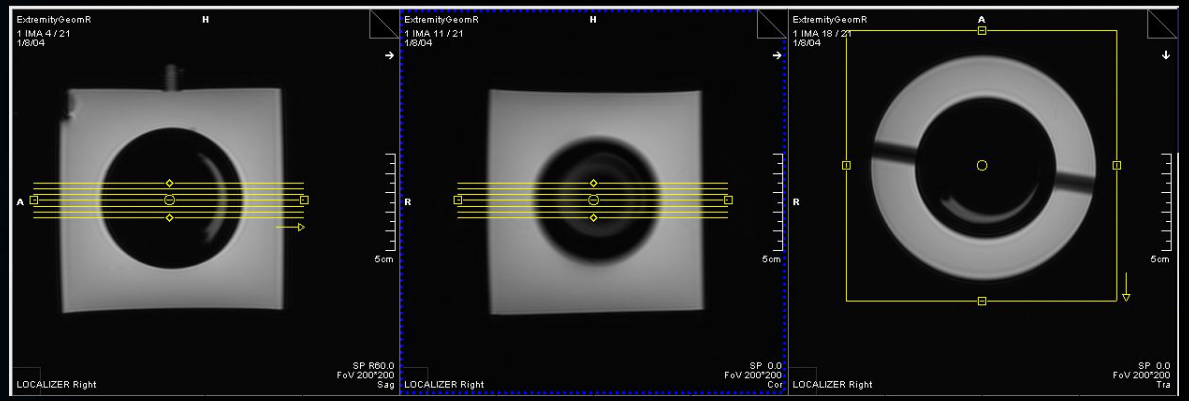
# Image Quality Control

- Imaging procedure manuals
- Central and local training of imaging personnel
  - Technologists
  - Local radiologists
- On-going technical feedback
- Site visits to qualify imaging facilities

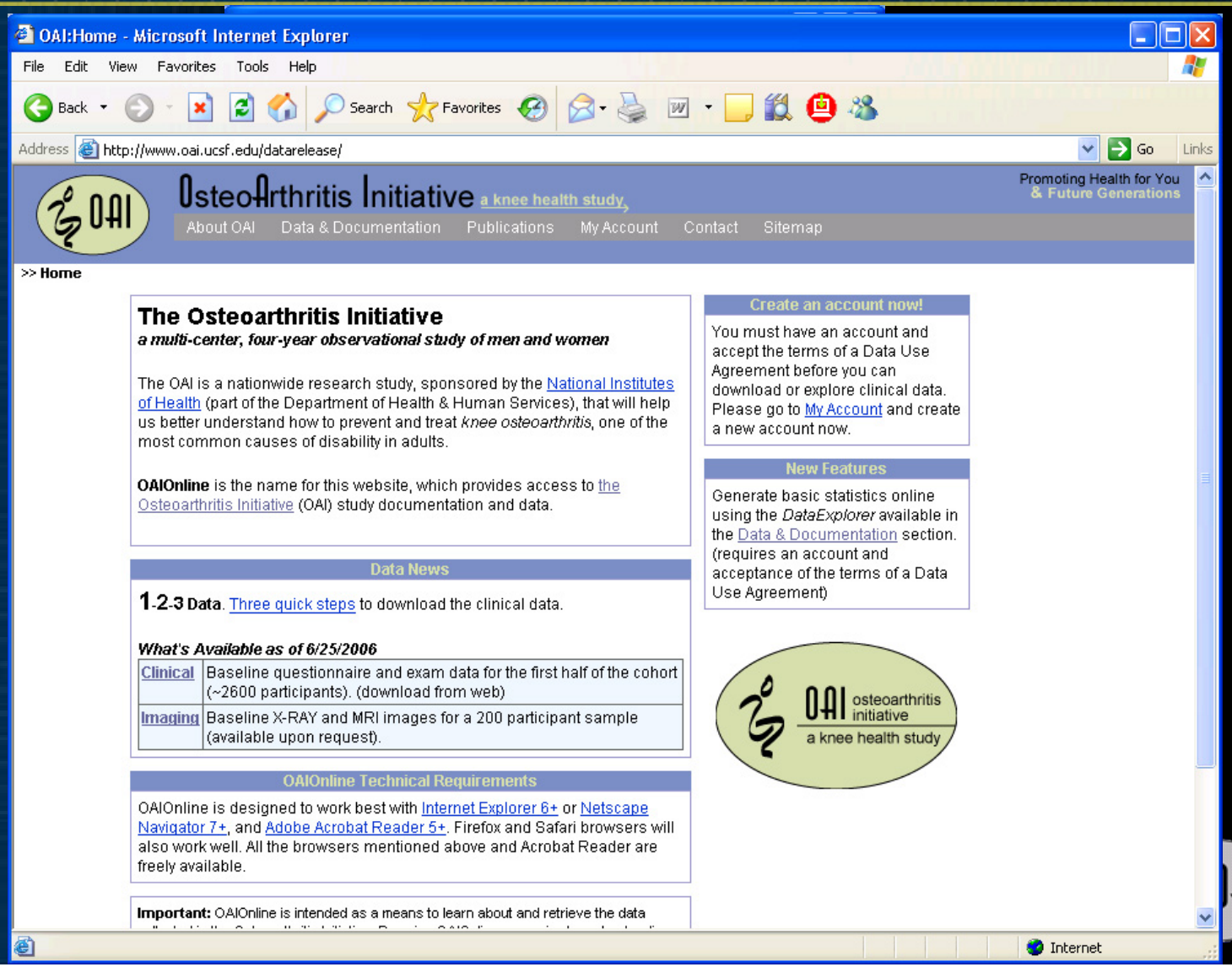
# Image Quality Control

- Acceptance testing
- MRI system performance monitoring
  - Phantoms (ACR and OAI)
  - Regular performance tests
- Image quality
  - Check for protocol adherence
  - Critical image quality criteria
    - Anatomical coverage
    - Artifacts
  - Feedback to sites



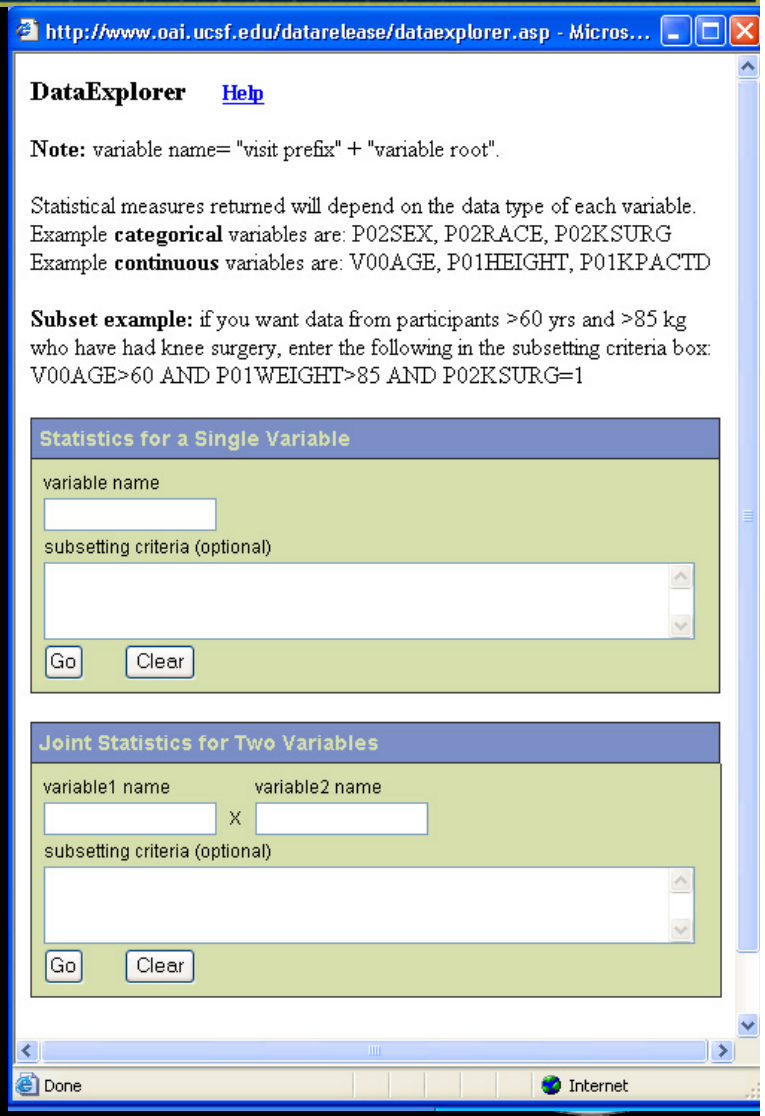


# Public Data Release
# http://w.w.w.oai.ucsf.edu/datarelease/



# Public Data Release
# http://w.w.w.oai.ucsf.edu/datarelease/

- General information about OAI and its design
- Description of study data, procedures and materials
- On-line access to forms, operating manuals and data documentation
- Limited on-line data exploration
- Clinical data sets available for download to registered users
- Images distributed on various electronic media
- Biospecimens available by application to NIAMS-administered Biospecimen Resource Allocation Committee



# Image Analyses

- OAI will make available a limited number of image assessments to address broad questions
  - Relationship between baseline structural and biochemical markers and risk factors with:
    - Onset or progression of X-ray JSW and MRI cartilage markers
    - Onset or progression of symptoms and disability
  - Relationship between changes in structural and biochemical markers with:
    - Onset or progression of X-ray JSW and MRI cartilage markers
    - Onset or progression of symptoms and disability

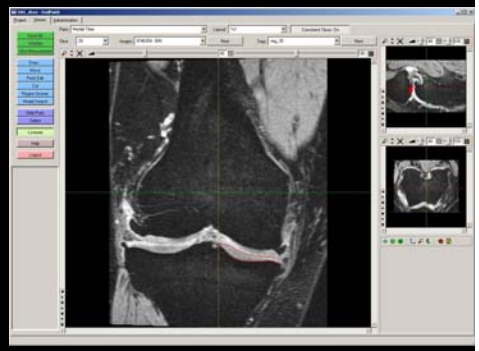
# Image Analyses

- Baseline radiographic assessments that were done by readers at the clinical sites to assign subcohorts
  - Presence of definite tibiofemoral osteophytes (OARSI 1-3)
  - Mild-moderate (OARSI 1-2) vs. servere (OARSI 3) medial tibiofemoral joint-space narrowing

# Image Analyses

- Central assessments of Progression subcohort TBD by Steering Committee and contracted out
  - Knee X-ray:
    JSW and subjective score at BL and FU →


  - Knee MRI:
    cartilage volume / thickness at BL and FU →
    semiquantitative score of OA features at BL



  - Hand X-ray:
    presence and severity of OA at BL
  - Pelvis X-ray:
    presence and severity of OA at BL

# The Osteoarthritis Initiative

- OAI represents a new research model:
  - Creation of public resources:
    - database, images & specimen repository
- Scientific partnership:
  - Academic and industry scientists
- Novel funding mechanism for research:
  - Involvement of multiple companies and NIH to pool resources
- Other consortia have since been established